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Original article

Impact of glutathione peroxidase and F2-isoprostane on mortality in anemic pediatric septic shock

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Abstract. *Background and aim:* Sepsis is a leading cause of morbidity and mortality in critically ill children worldwide. Studies show that pediatric septic shock mortality is higher when anemia is present. Increased oxidative stress, indicated by elevated F2-isoprostanes (F2-isoPs), is common in critically ill patients, but in anemia, antioxidant defenses are impaired, as shown by reduced glutathione peroxidase (GPx) levels. Despite these findings, only a few studies have specifically examined the role of anemia in pediatric septic shock through the lens of oxidative stress. This study aims to investigate the role of oxidative stress in children with septic shock, comparing those with and without anemia. *Methods:* A cohort of 30 children with septic shock, aged six months to 18 years, was monitored for three days. Hemoglobin levels, GPx, and F2-isoPs levels were measured daily. Statistical analysis was performed to compare the anemia and non-anemia groups. *Results:* Of all the samples, 15 children were anemic and 15 were not. Overall mortality was 70%. Hemoglobin and GPx level on the third day measurement showed a significant difference between survivors and non-survivors. The levels of GPx as a mortality predictor showed a sensitivity of 59% and a specificity of 60%, while GPx/F2-isoPs as a mortality predictor showed sensitivity of 59% and specificity of 62%. *Conclusions*: Anemia affects mortality in children with septic shock by decreasing antioxidant defense. (www.actabiomedica.it)

Key words: septic shock, anemia, oxidative stress, glutathione peroxidase, F2-isoprostanes

Introduction

Sepsis is one of the leading causes of morbidity and mortality in critically ill children worldwide. Globally, sepsis occurs in 22 children per 100,000 children per year. The mortality rate of critically ill pediatric patients with sepsis ranges from 4–50%, depending on disease severity, risk factors, and geographic location (1). In Indonesia, the death rate due to septic shock remains quite high, at 88.2% (2). Premorbid factors that affect the outcome of children with sepsis include their specific age, nutritional status, and anemia. Malnutrition increases mortality 4-fold, while anemia increases mortality 3-fold (3). Anemia often develops during the clinical course of sepsis and becomes a complication in the management of sepsis (4). Administration of intravenous resuscitation fluids can affect hemoglobin (Hb) levels, leading to a decrease in Hb levels (5). Studies in India show that septic children often present with low hemoglobin (Hb), typically below 7 g/dL (6). Studies in Africa indicate that pediatric patients with septic shock who receive resuscitation while having low Hb levels exhibit higher mortality (7). To date, there have been few studies explaining the role of anemia in the progression of septic shock. Severe sepsis has traditionally been understood as an uncontrolled inflammatory process triggered by an infectious agent. The presence of cytokine stimulation, immune cells, and

endothelial cell injury stimulates an increase in reactive oxygen species (ROS). High ROS levels affect blood circulation and endothelial cells, causing damage at the cellular level. Oxidative stress in septic conditions has more serious consequences in pediatric patients than in adults due to their lower functional reserve capacity and the need for tissue growth (8). F2-isoprostanes (F2-isoPs), a marker of oxidative stress in septic patients with circulatory failure, are also elevated due to lipid peroxidation (9). F2-isoPs have advantages in detecting oxidative stress, including being specific for lipid peroxidation, not affected by lipid intake, detectable in biological fluids, and easily measured by non-invasive methods, including in urine, plasma, and tissues (10). In response to increased oxidative stress, the human body typically elevates plasma antioxidant capacity. During septic shock, however, the balance between the production of ROS and their neutralization by antioxidants is disrupted, leading to increased oxidative stress (11). Among the body's endogenous antioxidant defenses, glutathione is the most abundant and plays a critical role, but it has been shown to be depleted during critical illness. Glutathione peroxidase (GPx) is a crucial antioxidant enzyme that plays a key role in reducing inflammation and tissue damage caused by ROS generated by phagocytes (12). A study by Tekin et al. showed that pediatric patients with anemia not only have increased oxidative stress, as evidenced by higher levels of malondialdehyde, but also exhibit decreased antioxidant defense, as indicated by lower GPx levels (13). However, few studies have evaluated in detail the role of anemia in children with septic shock through the lens of this imbalance between oxidative stress and antioxidant defense. Therefore, this research is expected to be useful for clinicians in predicting outcomes and improving the management of children with septic shock.

Methods

This study is a prospective cohort study that enrolled critically ill children with sepsis who were treated in the inpatient unit, pediatric intensive care unit (PICU), and emergency department at Dr. Soetomo Regional Hospital from August 2020 to February 2022. The parents of the patients were required to sign informed consent after the researchers provided an explanation regarding the importance of the study. The study received approval from the Ethics Committee of the Faculty of Medicine at Universitas Airlangga - Dr. Soetomo General Hospital. This study included two groups: one with septic shock and anemia, and one without anemia. The sample size was determined using the resource equation method, with a total of 30 children—15 in the septic shock with anemia group and 15 in the septic shock without anemia group. A study by Aslan et al. found that critically ill children with iron deficiency anemia experience increased oxidative stress, with its intensity correlating to anemia severity, particularly when hemoglobin levels fall below 7.5 g/dL (14). Therefore, we defined the anemia group as having a hemoglobin level <7.5 g/dL at the first day. First, basic demographic data were collected. PELOD-2 (Pediatric Logistic Organ Dysfunction-2) scoring was also measured to determine organ dysfunction and disease severity in critically ill children. Blood samples were then drawn from critically ill pediatric patients into 5 ml Venoject tubes with EDTA anticoagulant. Samples were collected on the first, second, and third days after fluid resuscitation. Patients who died within 48 hours were excluded. Several variables were tested from the blood samples, including hemoglobin, F2-isoprostane and glutathione peroxidase (GPx). F2-isoPs and GPx were measured using an enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems/Biotechne, United Kingdom, and the data obtained are presented on a ratio scale. The Shapiro-Wilk test was used to assess the normality of numerical data. For normally distributed data, results are presented as means with standard deviations (SD), while non-normally distributed data are presented as medians with the corresponding minimum and maximum values. Nominal data were analyzed using the Chi-square test. For normally distributed numerical data, the t-test was used, while the Mann-Whitney test was applied to non-normally distributed numerical data. Bivariate analysis was performed to assess correlations between variables: Pearson's test was used for normally distributed data, and Spearman's test for non-normally distributed data. A receiver operating characteristic (ROC) curve was employed to

determine the optimal severity level cut-off score for predicting mortality outcomes. Sensitivity and specificity were calculated to identify the cut-off point associated with mortality prediction.

Results

Subjects' characteristics

Characteristic of the research subjects are shown in Table 1. A total of 30 patients who met the study criteria were included, of whom 21 died and 9 survived. No subjects were excluded during the study period. The comparison between septic shock with and without anemia showed no statistically significant difference in the PELOD-2 score. The correlation between septic shock with and without anemia and mortality showed no statistically significant difference when analyzed as nominal data (with anemia and without anemia as independent variables and mortality as the dependent variable). Additionally, we conducted statistical analysis on anemia, measured by hemoglobin levels as numerical data, in relation to the mortality outcome, as shown in Table 2.

Correlation between hemoglobin level and outcome

Table 2 presents serial measurements of hemoglobin levels in the survivor and non-survivor groups. Hb levels were lower in the non-survivor group than in the survivor group across all three days of observation. The data also indicate a correlation between hemoglobin (Hb) levels, as a marker of anemia, and mortality outcomes. Specifically, Hb levels show a significant correlation with mortality outcomes on the third day of observation.

Serial trend of biomarker levels of F2 Isoprostane and Glutathione Peroxidase in anemia and non-anemia group

Trends in the serial levels of F2-isoPs and GPx, as well as the differences between the anemic and non-anemic groups, are presented in Table 3. The correlation between F2-isoPs and GPx levels in both groups showed no significant correlate when analyzed as nominal data (anemia vs. non-anemia). As a continuation, we also conducted a statistical analysis to examine the relationship between anemia, as indicated by hemoglobin levels (using numerical data), and F2-isoPs and GPx.

Correlation between F2 isoprostane and glutathione peroxidase

The GPx levels as an antioxidant biomarker were significantly negatively correlated with the F2-isoPs levels as a stress oxidative biomarker ($r = -0.217$, $p=0.040$) (Table 4).

Correlation between hemoglobin level to overall oxidative stress biomarker.

The correlation between Hb levels as a marker of anemia and the oxidative stress variables is confirmed

Table 1. Characteristics of subjects in septic patients with and without Anemia

Characteristics	Septic shock with anemia n(%)	Septic shock without anemia n (%)	p value
Gender (n%) Male Female	 5 (16.67) 10 (33.33)	 8 (26.67) 7 (23.33)	 0.398[x]
Age (months)	120 (9-192)[b]	36 (12-204)[b]	0.208[y]
Hemoglobin levels (g/dl)	5.72 ± 1.36[a]	9 (7.50-12.50)[b]	**0.000[y]***
PELOD-2 score	8 (5-20)[b]	10.67 ± 3.33[a]	0.076
Outcome Survivor (n%) Non Survivor (n%)	 5 (16.67%) 10 (33.3%)	 4 (13.33%) 11(36.67%)	 0.500[x]

[a]Mean ± SD; [b]Median (min-max); [x]Chi-square test; [y]Mann–Whitney test *significant ($p < 0.05$).

Table 2. Measurement of serial hemoglobin parameters and their correlation with mortality outcomes

Variable	Serial parameters	Survivor (n=9)	Non-Survivor (n=21)	p value
Hemoglobin levels (g/dl)	Day-1	7.57 ± 2.86	8.76 ± 2.49	0.722 [a]
	Day-2	12.6 ± 2.90	10.70 ± 2.71	0.963 [a]
	Day-3	10 (9.10-14.60)	9.10 (6.10-12.20)	**0.002*[b]**

[a]Independent sample T test
[b]Mann-Whitney U test *statistically significant (p<0.05)

Table 3. Measurement of variables in day 1, 2, and 3 and their correlation with anemia

Variables	Septic shock with anemia	Septic shock without anemia	p value
F2 isoprostane (pg/ml)			
Day 1 median (min-max)	151.4 (41.5-389.64)	258.82 (31.16-1522.90)	0.206[b]
Day 2 median (min-max)	180.54 (20-1830.80)	250.90 (116.39-435.28)	0.663[b]
Day 3 median (min-max)	226.71 (14-1926.20)	245.59 (81.80-436.60)	0.494[b]
Glutathione peroxidase (ng/ml)			
Day 1 Median (min-max)	20.72 (13.58-1593.72)	18.05 (13.80-11.285.89)	0.694[b]
Day 2 Median (min-max)	17.50 (13.80-4902.60)	21.95 (15.85-10504.14)	0.885[b]
Day 3 Median (min-max)	36.18 (15.50-2958)	19.66 (1.92-12.092.39)	0.290[b]

[a]Independent sample T test
[b]Mann-Whitney U test *statistically significant (p<0.05)

Table 4. Correlation between F2 isoprostane and glutathione peroxidase

	F2 Isoprostane (ng/ml)	
Marker	**r value**	**p value**
Glutathione peroxidase (ng/ml)	-0.217	**0.040 [d*]**

[d]Spearmann correlation test, *statistically significant (p<0.05)

in Table 5. It can be seen that Hb does not significantly correlate with F2-isoPs levels as a marker of oxidative stress, GPx as a marker of antioxidant defense, and GPx/F2-isoPs ratio.

Overall oxidative stress biomarkers serial measurement and their correlation with mortality outcomes

The measurement of serial levels of F2-isoPs, GPx, and GPx/F2-isoPs ratio in relation to mortality outcomes is presented in Table 6. There were no statistically significant differences in F2-isoPs levels between the survivor and non-survivor groups. The levels of GPx on the first and second days did not differ between the survivor and non-survivor groups. However, on the third day, the levels of GPx were lower in patients who did not survive septic shock compared to those who survived and has a significant correlation (19.6 vs 141.1 ng/ml, p = 0.002). In line with

GPx levels, GPx/F2-isoPs ratio on the first and second days did not differ between both groups, but has a significant correlation on the third day (0.08 vs 0.15, p = 0.011)

Antioxidant levels, as indicated by GPx levels, showed significant differences in relation to the mortality of pediatric critically ill patients with septic shock. Based on the ROC curve analysis, the cut-off value of 23.56 ng/ml for GPx in relation to mortality showed a sensitivity of 59% and a specificity of 60%, with an AUC of 0.67. The unbalance of stress oxidative event and antioxidant defense shown by GPx/F2-isoPs ratio showed a sensitivity of 59%, specificity of 62%, with an AUC of 0.68 in predicting mortality (Figure 1).

Table 5. Correlation between Hb level with overall oxidative stress

Marker	Correlation with Hb level (p value)
Glutathione peroxidase (ng/ml)	0,056[e]
F2 isoprostane (pg/ml)	0,747[e]
Glutathione peroxidase/ F2 Isoprostane Ratio	0,218[e]

[e]Pearson correlation test

Discussion

In this study, the organ dysfunction score, represented by the PELOD score, did not differ significantly between pediatric septic shock patients with and without anemia. This contrasts with a study by Sarah et al., which found higher PELOD-2 scores in anemic patients (15), and Rusmawatiningtyas et al., who reported a higher mortality rate (88.2%) associated with elevated PELOD scores (12 in survivors vs. 22 in non-survivors) (16). However, we found a significant correlation between hemoglobin levels (as a marker of anemia) and mortality, aligning with Ortega et al., who observed a 14.8% mortality risk in sepsis patients, with a higher incidence in anemic patients (10.5% vs. 15.3%, p = 0.204). Anemic patients also had

Table 6. Measurement of serial parameters of glutathione peroxidase and F2 isoprostane to mortality outcomes

Variable	Serial parameters	Survivor (n=9)	Non-Survivor (n=21)	P value
***F2 isoprostane*, pg/ml**	Day-1	254,83 (43.17-1522.90)	183,35 (31.16-807.11)	0.309[b]
	Day-2	179.2 (116.39-420.80)	250.90 (20-1830.80)	0.910[b]
	Day-3	359.69 (81.80-474.45)	222,57 (14-1926,20)	0.353[b]
***Glutathione peroxidase*, ng/ml**	Day-1	23.52 (13.58-11.285.89)	19.93 (13.8-1.593.72)	0.541[b]
	Day-2	40.19 (14.59-10504.14)	17,50 (13.80-993.97)	0.402[b]
	Day-3	141.14 (17.69-12092.39)	19,60 (1.92-177.49)	**0.002**[b*]
Glutathione peroxidase/F2 Isoprostane Ratio	Day-1	0,38 (0,01- 48,72)	0,13 (0,02- 11,64)	0,824[b]
	Day-2	0,15 (0,04- 33,89)	0,09 (0,01- 10,83)	0,193[b]
	Day-3	0,15 (0,04- 33,89)	0,08 (0,01- 12,68)	**0,011**[b*]

[a] *Independent sample T test*
[b] *Mann-Whitney U test*
*statistically significant (p<0.05)

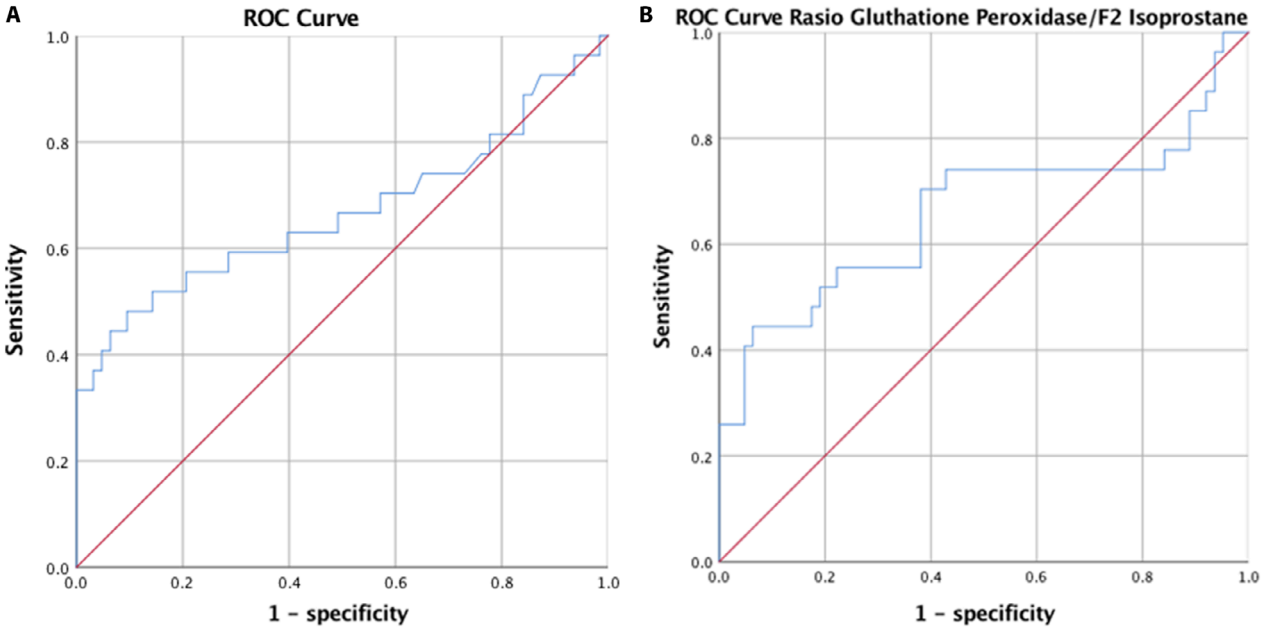

Figure 1. ROC curve for (A) GPx levels and mortality with cut-off of 23,56 ng/mL, sensitivity 59%, and specificity 60%; (B) GPx/F2-isoPs ratio and mortality with cut-off of 0.16; sensitivity of 59%; and specificity of 62%.

a significantly longer length of stay (24.6% to 68.1% longer, $p < 0.001$) and higher treatment costs (61.2% more expensive) (17). Oxidative stress, measured by F2-isoPs, did not correlate with an anemic state in children with sepsis in this study. However, hemoglobin levels, as a marker of anemia, tend to affect the antioxidant marker, as shown by glutathione peroxidase ($p = 0.056$). Some studies have shown a positive relationship between hemoglobin levels and antioxidant activity, possibly due to hypermetabolic conditions in sepsis that increase energy demands and result in the accumulation of cellular toxins (H_2O_2, xanthine oxidase, and lipid peroxidation) from increased electron transport chain activity (18). Anemia in sepsis occurs due to decreased production of erythropoietin due to the release of pro-inflammatory cytokines, Interferon gamma (IFNγ) and IL-1, which inhibit the growth of pro-erythrogenic cells and act as precursors of apoptosis in erythroid so that anemia develops (19). The accumulation of metabolic toxins causes pathological conditions that lead to organ dysfunction. In controlling metabolic toxins, the body produces antioxidants to clean these toxins. H2O2 is degraded to water by glutathione peroxidase (GPx). The glutathione peroxidase used during this process must be replenished so that it does not accumulate to levels that cause toxicity. However, GPx refilling cannot be done during the hypermetabolic period, so within 48 hours after the diagnosis of sepsis, GPx levels decrease by up to 60% (20). In a study of anemic dogs, Kendall et al. found lower GPx activity in anemic dogs ($p < 0.001$), with no significant difference between hemolytic and non-hemolytic anemia ($p = 0.570$) (21). A significant correlation between PCV and GPx activity was noted in these animals ($r = 0.878$; $p < 0.001$). Similar findings have been reported in diabetic patients, where reduced GPx, glutathione reductase, and glutathione levels correlate with lower hemoglobin concentrations, red blood cell counts, and markers (MCV, MCH, MCHC) (22). In our study, GPx levels were significantly negatively correlated with F2-isoPs levels, indicating reduced antioxidant defense against oxidative stress in children with sepsis. In septic shock, uncontrolled inflammation increases reactive oxygen species (ROS), which damage endothelial cells and disrupt blood circulation, leading to cellular dysfunction. This, in turn, impairs mitochondrial respiration and promotes anaerobic metabolism. Initially, antioxidants may

effectively counteract oxidative stress, but as sepsis progresses, anaerobic processes reduce GPx activity (23). We also found a significant correlation between GPx levels and mortality, consistent with Semedi's study, which showed that in critically ill patients with vasodilatory shock, reduced GPx activity is linked to tissue hypoxia, organ failure, and higher mortality (24). Additionally, the GPx/F2-isoPs ratio correlated with mortality, suggesting that the imbalance between oxidative stress (represented by F2-isoPs) and antioxidant defense (indicated by GPx) worsens the severity of septic shock and contributes to increased mortality.

Study's limitation

The limitations of this study include the lack of analysis of hemoglobin levels, which were correlated with mortality, in relation to oxidative biomarkers (F2-isoPs and GPx levels). Additionally, we did not assess lipid peroxidation using other markers, as F2-isoPs may not be an ideal marker in the acute phase of sepsis. We also did not evaluate other inflammatory markers that could influence oxidative stress in septic shock. In conclusion, further research is needed to identify the most accurate biomarkers and their optimal cut-off values for predicting 28-day mortality in sepsis, as this remains controversial due to the variety of markers used.

Conclusion

Anemia influences mortality in children with septic shock by impairing antioxidant defense, as shown by the correlation between hemoglobin concentration, glutathione peroxidase activity, and mortality. GPx levels vary between groups and may serve as a mortality predictor. Further research is needed to explore inflammatory markers and other factors that may impact oxidative stress in septic shock.

Ethic Approval: The patient's parent must sign the informed consent after the researchers have provided an explanation regarding the importance of the study. This study was approved by the Ethical Committee of the Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Hospital (ethical clearance number 0166/105/3/VIII/2020).

Conflict of Interest: The authors declare that they have no commercial associations such as consultancies, stock ownership, equity interest, patent/licensing arrangement, that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: AS: Concept and study design, literature search, clinical studies, data acquisition, data and statistical analysis, manuscript preparation; S, AE, AHP: Concept and study design, supervising; ID, NPK, DPL: Literature search, clinical studies, data acquisition, data and statistical analysis. All authors approved the final version and are accountable for the work's accuracy and integrity.

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